Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP CAP

Submission number: 12601A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

~~STOX~~ SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	~~NEUR~~

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 (1) 2 **pages** 1,2 **pages** 1,2, tab

Notes:

Contractor reviewer : LPS **Date:** 5/11/95

(1)

RHÔNE-POULENC

TOXICOLOGY DEPARTMENT
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE
RESEARCH TRIANGLE PARK, NC 27709
(919) 549-2000 TELEFAX (919) 549-8525
INTERNATIONAL TELEX NUMBER 4999378-ANSWERBACK APC RTP

92 SEP 21 AM 7:58

September 14, 1992

(A)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
P 713 002 910

8EHQ-92-12601

8920010785

INIT

Document Processing Center (TS-790)
Office of Toxic Substances
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company, the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on chlormephos. The CAS number assigned to this compound is 24934-91-6. The CAS name is S-(chloromethyl) O,O-diethyl phosphorodithioate. This chemical was manufactured in Europe and imported for pesticide research and development. To our knowledge, a pesticide application on this chemical has never been submitted to EPA under the Federal Insecticide, Fungicide, and Rodenticide Act.

No claims of confidentiality are made for this submission. The title of the enclosed report is "The Acute Toxicity and Neurotoxicity of P2188 in the Domestic Hen". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of the observed clinical signs. The acute oral LD50 in hens of the material diluted with ethyl acetate was 130 mg/kg. The LD50 of the undiluted material was approximately 65 mg/kg. Death occurred usually 30 minutes to 18 hours, and never later than 48 hours after dosing. Signs of toxicity were characteristic of organophosphorus poisoning and included lethargy and slow, gasping respiratory movements. No signs of delayed neurotoxicity were seen in any of the birds at any stage of the experiment.

One previous TSCA Section 8(e) notice was submitted on this chemical on August 31, 1978. We do not have an EPA Document Control Number for this submission in our records. In addition, approximately 15 submissions will be made on chlormephos under the CAP.

mm
3/16/95

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,

Glenn S. Simon, PhD, DABT
Director of Toxicology

Contains NO CBI

CONFIDENTIAL

2859/69/285

THE ACUTE TOXICITY AND NEUROTOXICITY OF P2188 IN THE DOMESTIC HEN

Dr. V. H. Chambers,
Murphy Chemical Co. Ltd.,
Wheathampstead,
St. Albans,
Herts.

D. Robinson
K. W. G. Shillam

Huntingdon Research Centre,
HUNTINGDON

25 July, 1969.

S U M M A R Y

1. The acute oral toxicity and neurotoxicity in hens of the organo-phosphorus compound known as P2188 were investigated.

2. The acute oral LD_{50} of P2188, when dissolved in ethyl acetate and administered as a single dose into the crop, was found to be approximately 130 mg/kg. When the compound was administered in undiluted form the LD_{50} value was about 50-75 mg/kg.

3. No signs of neurotoxicity were observed in hens given two doses of P2188, each at the approximate upper LD_{50} level (125-160 mg/kg), and separated by a 21-day interval.

I N T R O D U C T I O N

P2188 is an organo-phosphorus compound having the chemical name:

O,O-diethyl-5-chloromethylphosphorothiolthionate

Oral LD_{50} values for the rat and the guinea-pig are reported as 7 and 14 mg/kg respectively (Dr. V. H. Chambers, Murphy Chemical Co. Ltd: letter dated 20 February 1969).

The objects of the present study were:

(a) to establish the acute oral LD_{50} of P2188 to the hen,

(b) to find whether the compound is capable of inducing in hens a delayed neurotoxic response like that produced by many other organo-phosphorus compounds.

For the second part of the study the procedure adopted was similar to that recommended by the Ministry of Agriculture in the Pesticides Safety Precautions Scheme (Working Document No. 2, Appendix B). This involves dosing adult hens with the compound at the approximate LD_{50} level and observing three or more survivors for clinical signs of neurotoxicity. If no symptoms occur after 21 days, the birds are again dosed at the LD_{50} level and observed for a further 21 days.

P R O C E D U R E

White Leghorn laying hens, eleven months of age, were used throughout these tests. They were housed in large floor-pens in a controlled-environment poultry building, with wood shavings as litter on the floor. Food and water were supplied ad lib.

No information on a suitable carrier for P2188 was supplied. Of the usual carriers examined, ethyl acetate appeared to be the most suitable and, except where otherwise indicated below, this was used for all dose tests.

LD_{50} value

Using the LD_{50} values reported for rats and guinea-pigs as a guide (see Introduction), preliminary range-finding doses were administered to each of two hens at levels of 5, 10 and 20 mg/kg. As little or no effect was produced at these levels, further pairs of hens were dosed at 40, 80 and 160 mg/kg. The results of these tests (summarized in Table 1, part 1) indicated that the hen LD_{50} is in the range 80-160 mg/kg. Groups of hens were therefore dosed with 80, 100, 125, 160 or 200 mg/kg (Table 1, part 2), the latter level being included in view of the high survival rate obtained at lower levels.

At this stage it was thought that there might be a dilution effect on the appearance of acute signs and mortality rate. In range-finding tests at levels of 40-160 mg/kg in which the rate of dilution with ethyl acetate was lower than that used in later assays, pronounced symptoms occurred at lower dose levels. To obtain more information on this possibility, hens were given single doses of undiluted P2188 at levels of 50, 75 and 110 mg/kg (Table 1, part 3). This test indicates that undiluted P2188 produces a toxic effect similar to that resulting from approximately twice the amount of material when diluted with ethyl acetate.

Neurotoxicity

For observations of neurotoxic effect three to six birds dosed at the approximate LD_{50} level are required. The two survivors at the 125 mg/kg level and one at the 160 mg/kg level were retained for this test. The single survivor at the 120 mg/kg level was not used as it was considered unsuitable and was subsequently shown at autopsy to be affected by peritonitis. In order to increase the number of birds available for observation, four additional hens were orally dosed with diluted P2188 at 140 mg/kg (Table 1, part 4). As three of these died, a dose of 125 mg/kg P2188 was administered to a fifth bird, which survived. Thus altogether five birds, dosed with 125-160 mg/kg P2188, were kept for observation. Four hens, dosed with ethyl acetate, served as the control group.

Twenty-one days after dosing, the test birds were re-dosed with 140 mg/kg P2188 and the controls were re-dosed with ethyl acetate. All the birds were injected intramuscularly with 1 mg/kg atropine sulphate and 100 mg/kg 2-hydroxyiminomethyl-N-methyl-pyridinium methanesulphonate to reduce the cholinesterase-inhibiting effects of P2188. After the second dose, the birds were kept for a further twenty-one days. During the period 8-21 days after each dose they were examined daily for signs of neurotoxicity. Individual body weights were recorded at the time of dosing and at termination of the experiment forty-two days after administering the initial dose.

R E S U L T S

Acute toxicity

The results of those assays in which P2188 was diluted with ethyl acetate to give a dose volume of 0.5-1.0 ml (Table 1, parts 1, 2 and 4) indicate that the acute oral LD_{50} to the hen is approximately 130 mg/kg. When P2188 was given undiluted an LD_{50} in the region of 50% of this value was indicated (Table 1, part 3). These values apply to light-breed laying hens allowed unrestricted access to food and water.

Deaths occurred usually 30 minutes to 18 hours, and never later than 48 hours, after dosing. Signs seen in birds dosed at high levels, without protection against cholinesterase inhibitors, were typical of organo-phosphorus poisoning and included lethargy and slow, gasping respiratory movements; some birds subsequently lost weight (see Table 2).

Oral administration of 1 ml/kg ethyl acetate usually produced an immediate, slight, transient lethargy; at 0.5 ml/kg this effect was barely noticeable.

Neurotoxicity

No signs whatsoever of delayed neurotoxicity were seen in any of the birds at any stage of the experiment.

T A B L E 1

Mortality rates

Dose level mg/kg	Dilution rate with ethyl acetate (ml soln./g P2188)	Symptoms of acute organo-phosphorus poisoning	Number of deaths/number of birds dosed
1. Preliminary range-finding tests			
5	100	none	0/2*
10	50	none	0/2*
20	25	slight	0/2
40	12.5	moderate	0/2
80	6.25	severe	1/2
120	4.5	severe	1/2
160	3.0	severe	2/2
2. Supplementary assays to determine LD_{50}			
80	12.5	moderate	0/2
100	10	moderate to severe	0/4
125	8	severe	2/4
160	6.25	severe	1/2
200	5	severe	2/2
3. Tests with undiluted P2188			
50	0	moderate	0/2
75	0	severe	2/2
110	0	severe	1/1
4. Additional birds dosed for neurotoxicity screening			
0	-	none	0/4
125	8	severe	0/1
140	8	severe	3/4

* These birds were subsequently re-used in tests employing dose levels higher than 100 mg/kg (not more than one bird at a given level).

T A B L E 2

Body weight changes of birds kept for observation of neurotoxic effect*

Hen no.	Initial dose, mg/kg	Initial body wt., g	Body weight changes, g:		
			0-21 days	21-42 days	0-42 days
146	125	2040	+ 10	+ 80	+ 90
916	125	1810	-160	+ 60	-100
12	140	2160	- 60	-190	-250
515	140	1650	-140	+110	- 30
681	160	2200	-360	-110	-470
51	0	1830	- 30	- 20	- 50
53	0	2440	+ 50	+ 10	+ 60
863	0	1580	+130	- 60	- 70
868	0	1740	- 20	+ 50	+ 30

* The five test birds were re-dosed with 140 mg/kg P2188 at 21 days after the initial dose; at this stage they were protected against cholinesterase inhibition.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0992 -12601 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Rhone - Poulenc

Inc.

SUB. DATE: 09/14/92 OTS DATE: 09/21/92 CSRAD DATE: 03/16/95

CHEMICAL NAME:

Chlormephos

phosphorodithioate, S-(chloromethyl)

O,O-diethyl

CAS#

24934-91-6

11

INFORMATION REQUESTED: FLWP DATE:

0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:

(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:

(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER ACTIVITY
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
(0209)	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
(0220)	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
(0224)	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
(0248)	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY
YES
CAS SR
NO
IN TERMINI

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
HEN

TOXICOLOGICAL CONCERN:
LOW
MED
HIGH

USE:
R:D
pesticide

PRODUCTION:
import

COMMENTS